# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Recent Advances in the Treatment of NASH

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### G&H What is the difference between nonalcoholic fatty liver disease and nonalcoholic steatohepatitis?

**SC** Nonalcoholic fatty liver disease (NAFLD) is an umbrella term referring to any fatty liver condition arising without association to alcohol exposure. Occasionally the difference between alcohol-related and nonalcohol-related fatty liver disease is not clear, but the majority of the time, individuals with fatty liver conditions who consume less than a certain threshold amount of alcohol are considered to have NAFLD.

Within NAFLD is a range of conditions, from types 1 (simple, or "pure" steatosis) and 2 (steatosis with mild inflammation) NAFLD to types 3 and 4, which are characterized by the presence of ballooning and/or fibrosis. Types 3 and 4 are also known as nonalcoholic steatohepatitis (NASH) (ballooning of a hepatocyte and fibrosis generally occur together).

### G&H What is the alcohol consumption threshold below which an individual is considered to have NAFLD rather than alcohol-related disease?

**SC** This amount is usually up to 20 grams per day; one can of beer, glass of wine, or shot of liquor has approximately 10 grams of alcohol. Consumption of less than 20 grams per day of alcohol is generally not sufficient exposure to explain fatty liver disease but there is wide variation in this threshold between individuals and between genders.

Interestingly, an individual who abstains from alcohol completely may be at greater risk for NAFLD than an individual who drinks modestly. This phenomenon probably relates to some beneficial indirect effect of mild exposure to alcohol on insulin signaling. There are data from patients with type 2 diabetes indicating that modest alcohol exposure improves insulin signaling.

### G&H What characteristics might indicate a high risk of developing NASH?

**SC** The major risk factors for NASH are obesity, type 2 diabetes, and hyperlipidemia. The obesity that puts a person at risk for NASH may not be general obesity. Individuals with central obesity have a greater risk of having fat stored in the viscera, including the liver; however, there appears to be a significant genetic influence with this risk factor that is reflected in ethnicity. African Americans tend not to store much fat in the liver compared to Americans of primarily European, Mexican, or Hispanic descent. Mexican Americans and European Americans have the highest rates of NASH in the United States; African Americans have a comparatively low incidence. The reason behind this difference is not clearly understood.

### G&H What are the nonpharmacologic therapies for NASH?

**SC** In general, the first line of therapy is exercise and diet. There are growing data indicating that even a modest amount of weight loss, say 14 pounds, can reduce the amount of fat in the liver, which appears to be the driving problem behind NASH.

Dietary composition is also an important consideration. There is some evidence that carbohydrate loading may be especially problematic. Thus, foods with high amounts of corn syrup, products with high sugar content, and high-starch foods may be particularly dangerous. It is important to be aware that it may not be just the total calorie intake that leads to NASH but the types of calories. Carbohydrate calories may be more highly associated than protein or fat calories with NASH development. This consideration raises the question of whether an Atkins-type diet would be advisable. There are not yet enough data to determine whether such an approach would be beneficial, but studies are underway.

Fatty acid composition is also important. It may be that a diet rich in polyunsaturated fats, such as fish oils, may be better than a diet rich in saturated fats. However,

it is important to note that a diet rich in polyunsaturated fats coupled with too much alcohol can lead to oxidative stress in the liver. Thus, there must be the correct balance in terms of all food and alcohol being ingested, and this balance may depend on the antioxidant status of the patient.

### G&H Is it possible to measure a patient's antioxidant status?

**SC** It is possible to measure oxidant stress, but such measurements are unlikely to be very accurate. In general, antioxidant status hinges on a person taking in good micronutrients through a range of foods including plenty of colored fruits and vegetables, which are generally rich in antioxidants.

### G&H Is bariatric surgery performed for patients with NASH?

**SC** For carefully selected patients, bariatric surgery may be a beneficial approach. Eligible patients are typically young adults less than 40–50 years old with a body mass index of greater than 35, thus giving a favorable risk:benefit ratio. Bariatric surgery is a high-risk procedure associated with serious complications, but for a select group of patients it may be a good treatment approach.

### G&H Could you describe the various pharmacologic therapies that have been studied in NASH?

**SC** There are two main categories of pharmacologic agents that have been evaluated for NASH: antioxidant-cytoprotective agents and agents that affect insulin activity. In the former category, vitamin E can often normalize liver enzymes but has a variable effect on histology and therefore has been somewhat disappointing as a monotherapy. With the exception of betaine, other antioxidants, such as selenium and lipoic acid, have not been well studied. Among the cytoprotective agents, ursodeoxycholic acid (ursodiol) has also been found to consistently normalize liver enzymes, but, again, with a variable effect on histology. However, a controlled trial of ursodiol plus vitamin E showed promising results. In this study, reported at the 2005 annual meeting of the European Association for the Study of the Liver by Dufour and colleagues, 800 units of vitamin E were combined with 13–15 mg/kg ursodiol. The findings have not yet been published in a peer-reviewed journal to my knowledge.

Generally considered an insulin sensitizer (although technically it is not), metformin has been studied for the treatment of NASH. This agent appears to alter primarily skeletal muscle glucose utilization, enabling a person to burn off a greater amount of excess calories.

None of these agents have been approved by the US Food and Drug Administration for the treatment of NASH. There are some promising data in preclinical animal models, but the clinical data have been more variable. Metformin may have a role in pediatric NASH, but studies are needed to clearly determine its efficacy in that setting. The other major group of insulin sensitizers is the TZD group, or thiazolidinediones, such as pioglitazone and rosiglitazone. These agents appear to shift fat from visceral stores to peripheral fat stores, which appears to alleviate liver injury by removing the substrate for oxidative stress (the excess triglycerides). They may also affect the stellate cells, causing less fibrosis. However, these agents often cause weight gain and their liver benefit appears not to be sustained after discontinuing the agent. Clearly much more knowledge of how to apply these treatments is needed. Aside from fish oil, the TZDs are the only agents studied thus far that appear to remove fat from the liver.

### G&H Wouldn't the weight gain from TZD be harmful to someone with NASH?

**SC** While this weight gain might add to the overall obese condition of a patient, the peripheral distribution of fat seems to be somewhat safer. These agents might have a role in the treatment of patients that are showing evidence of significant progression, such as bridging fibrosis or cirrhosis. As long as there is an active component of steatohepatitis, such an individual would be a likely candidate for this therapy.

Both metformin and the TZDs are still in clinical trials for use in NASH. There has been one placebo-controlled trial of a TZD conducted thus far. Preliminary results, presented at the May 2005 American Gastroenterological Association annual meeting, were encouraging. A large trial comparing pioglitazone with placebo sponsored by the National Institutes of Health is currently in progress.

### G&H Could you further describe the potential mechanisms of action of the TZDs?

**SC** These agents appear to work through the removal of fat. The effect on the liver is most likely indirect. They may also have an effect on the stellate cells in the liver, which produce bad fibrosis material (collagen). TZDs may alter these cells in particular, as a direct effect on the liver.

### G&H What other types of agents are being evaluated for the treatment of NASH?

**SC** The HMG-coA reductase inhibitors, more commonly known as statins, are mainly promoted as cholesterol-lowering drugs, but they may have significant effects on NASH. The main site of action of these agents is the

liver, where they affect cholesterol synthesis. Given that the main problem with NASH is fat metabolism in the liver, there is most likely some interaction between NASH and cholesterol synthesis. However, there are differences of opinion regarding the use of statins in the treatment of NASH, and more data are needed.

**G&H** If any of the above-mentioned agents are proven to be effective, when might they be approved for use in NASH?

**SC** Large definitive studies are in progress now for metformin and pioglitazone. Completion of these trials is still a couple of years away, however, and an application for approval will probably not be made before then.

**G&H** With the numerous agents being studied, is there a concern that patients will rely too much on medication and will not focus on exercise and dietary changes?

**SC** This is a major concern, although there has been a fair amount of success with encouraging patients with NASH to exercise. Also, if a patient has developed fibrosis then pharmacologic therapy or bariatric surgery may be needed. For these patients, the risk that more aggressive approaches may reduce the motivation to exercise seems more acceptable; exercise or instructions to exercise have probably already failed.

**G&H** What are the challenges in interpreting studies in NASH?

**SC** There are two major unknown factors at play when interpreting the data from these studies. First, we do not know the change in lifestyle that was made by any particular patient. For example, if in a placebo-controlled trial all of the patients in the placebo group exercised and none of the patients in the control group exercised, the drug might not be shown to be of great benefit. Even though the drug was effective, the benefit will not show because the placebo patients were benefiting from increased exercise. Lifestyle change needs to be accounted for as a potentially confounding variable.

Also, liver biopsy is the gold standard for measuring efficacy. However, if the biopsy is too small, the effect might not be detected. It is important to know how big the biopsy was in any given study. Most study reports do not include this information, making it difficult to know if the analysis is correct or if the specimen might have been inadequate.

## Suggested Reading


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